

Diuretic Agents

Name	Site of Action	Mechanism of Action
Carbonic Anhydrase Inhibitor	Proximal tubule	Inhibit NaHCO_3 reabsorption
Loop Diuretics	Thick ascending limb of the loop of Henle	Block the $\text{Na}^+\text{K}^+/\text{2Cl}^-$ symporter
Thiazide Diuretics	Early distal tubule	Block the Na^+/Cl^- symporter
Potassium Sparing Diuretics	Late distal tubule and cortical collecting duct	Block Na^+ channels
Osmotic Diuretics	Thin descending limb of the loop of Henle and proximal tubule	Increase osmolarity of tubular fluid

1. Carbonic Anhydrase Inhibitors: **Acetazolamide**, **dorzolamide** (All compounds are sulfonamides).

<u>Renal effects</u>	<u>ROA</u>	<u>Therapeutic Uses</u>	<u>Adverse effects</u>	<u>Contraindications and Precautions</u>
<ul style="list-style-type: none"> • ↑renal excretion of: Na⁺, K⁺, HCO₃⁻ • ↓renal excretion of: NH₄⁺, H⁺. • Urine pH: alkaline. • Acid-base balance: metabolic acidosis (<i>acidosis is associated with hyperchloremia because Cl tend to exit from cells when H⁺ is high, in order to maintain electroneutrality</i>). • Efficacy of diuretic: low, moreover, as metabolic acidosis develops, the filtered load of HCO₃⁻ decreases, and therefore the diuretic effect undergoes a complete tolerance in 2-3 days) 	<p>Acetazolamide given PO,</p> <p>dorzolamide topical (eye drops)</p>	<ul style="list-style-type: none"> • Edema • Glaucoma (50-60% reduction in aqueous humor production) • Epilepsy (direct inhibition of carbonic anhydrase in the CNS, which increases carbon High altitude sickness) • Metabolic alkalosis 	<ul style="list-style-type: none"> • Paresthesias, drowsiness • Nephrolithiasis (due to precipitation of calcium phosphate salts in alkaline urine) • Hyperchloremic metabolic acidosis, Hyperuricemia, Hypokalemia • Sulfa-type allergic reactions 	<ul style="list-style-type: none"> • Hepatic cirrhosis (<i>alkalinization of urine decreases urinary trapping of NH₄⁺</i>) • Chronic obstructive pulmonary disease (<i>the risk of metabolic acidosis is increased</i>) • Hypersensitivity to sulfa drugs. • Hypokalemic states

2. Thiazide Diuretics : The most commonly used diuretics

Chlorothiazide, Hydrochlorothiazide, Bendroflumethiazide and Indapamide (All are sulfonamide)

<u>Renal effects</u>	<u>ROA+ Pharmacokinetics</u>	<u>Therapeutic Uses</u>	<u>Adverse effects</u>	<u>Contraindications and Precautions</u>
<ul style="list-style-type: none"> • ↑ renal excretion of: Na⁺, K⁺, H⁺, Cl⁻, HCO₃⁻. • ↓ renal excretion of: Ca⁺⁺, NH₄⁺, urates. • Urine pH: alkaline (due to inhibition of carbonic anhydrase). • Acid-base balance: metabolic alkalosis. • Efficacy of diuretic effect: moderate • Kidney diluting capacity: decreased • Duration of diuretic effect: variable (6-48 hours). <p><u>Other effects</u></p> <ul style="list-style-type: none"> • ↓ peripheral vascular resistance • ↓ cardiac output 	<p>PO, IM, IV.</p> <p>cross the placenta</p>	<ul style="list-style-type: none"> • Hypertension (first choice diuretics). • Edema and ascites associated with heart, liver and kidney disease • Calcium nephrolithiasis (idiopathic hypercalciuria). • Meniere's disease (they can prevent the endolymphatic fluid buildup) • Nephrogenic diabetes insipidus (<i>this seemingly paradoxical effect is likely mediated through the extracellular volume contraction which promotes proximal tubular reabsorption of Na⁺ and water. Therefore a reduced volume is delivered to the distal tubule</i>) 	<ul style="list-style-type: none"> • Hypokalaemia, metabolic alkalosis, hypovolaemia and hyponatraemia • Hyperuricaemia, Hyperglycaemia, Hyperlipidaemia, hypercalcemia • Hypotension • Hypersensitivity • Deterioration of patients with hepatic or renal failure • Paresthesia, drowsiness, fatigability • Impotence 	<ul style="list-style-type: none"> • <u>Contraindications</u> • Anuria • Sulfonamide hypersensitivity, thiazide diuretic hypersensitivity • <u>Precautions</u> • Hyperglycemia, Hyperuricemia (gout) , electrolyte imbalance

3. Loop diuretics

<u>Renal effects</u>	<u>ROA + Pharmacokinetics</u>	<u>Therapeutic Uses</u>	<u>Adverse effects</u>
<ul style="list-style-type: none"> • ↑ renal excretion of: Na⁺, Cl⁻, K⁺, H⁺, Ca⁺⁺, (sulfonamides also increase the excretion of HCO₃). • Acid-base balance: metabolic alkalosis. • The diluting and concentrating capacity of the kidney are decreased. • Efficacy of diuretic effect: high, moreover the diuretic effect remains even when the GFR is less than 30 mL/min). 	<p>PO, IM, IV. They have rapid onset of action Efficacy: High</p> <p>Given in ER</p>	<ul style="list-style-type: none"> • Acute pulmonary edema (given IV). Heart failure. • Edema, Ascites (associated with hepatic, renal and heart disease). • Hypertension (associated with renal insufficiency or heart failure). • Hypercalcemia. • (Addition of a thiazide can cause synergistic effect when a patient become refractory to a loop diuretic alone) 	<ul style="list-style-type: none"> • Ototoxicity: hearing loss • Hyperuricemia, Hyperglycemia, Hyperlipidemia • Hypotension • Hypokalemia, Hypomagnesemia, hyponatraemia

CONTRAINDICATIONS and PRECAUTIONS of LOOP DIURETICS	
Contraindications	Explanations
Serious hypovolemic or hyponatremic states.	Loop diuretics can cause hypovolemia and hyponatremia
Serious hypokalemic or hypocalcemic states.	Loop diuretics can cause hypokalemia and hypocalcemia
Severe diabetes mellitus	Loop diuretics can cause can cause hyperglycemia
Gout and hyperuricemia	Loop diuretics cause hyperuricemia

4. Potassium Sparing Diuretics

<u>Types according MOA</u>	<u>Therapeutic Uses</u>	<u>Contraindications and Precautions</u>
<ul style="list-style-type: none"> • <u>Aldosterone antagonists:</u> <ul style="list-style-type: none"> • Spironolactone, Eplerenone. • Spironolactone is a steroid drug. • <u>Direct Na⁺ - channel inhibitors :</u> <ul style="list-style-type: none"> • Triamterene , Amiloride. • Triamterene and amiloride are organic bases 	<ul style="list-style-type: none"> • Most commonly used in combination with other diuretics 	<ul style="list-style-type: none"> • <u>Absolute contraindications</u> <ul style="list-style-type: none"> • Hyperkalemia • Renal failure • <u>Precautions</u> <ul style="list-style-type: none"> • Gout • Pregnancy • Acid base imbalance

5. Osmotic diuretics

Mannitol i.v. infusion (25%), **Concentrated glucose i.v** (50%). **Glycerol**

<u>N.B</u>	<u>Therapeutic Uses</u>	<u>Adverse effects</u>	<u>Contraindications and Precautions</u>
<ul style="list-style-type: none"> • Loop Loose Calcium • Thiazide causes Hyper GLUC <ul style="list-style-type: none"> • Glycemia, Lipedemia, Uricemia, Calcemia • K⁺ sparing diuretics causes STAY of K⁺ 	<ul style="list-style-type: none"> • Acute oliguric RF: to maintain adequate GFR • Acute glaucoma: to ↓ aqueous humor formation • Increase intracranial tension: to ↓ CSF formation 	<ul style="list-style-type: none"> • Headache, nausea and vomiting are commonly observed • hypernatremia • Mannitol may cause hypersensitivity reaction. • Glycerol is metabolized and can cause hyperglycemia and glucosuria. 	<ul style="list-style-type: none"> • <u>Absolute</u> <ul style="list-style-type: none"> • Heart Failure, dehydration, intracranial bleeding • <u>Precautions</u> <ul style="list-style-type: none"> • Electrolyte imbalance, hypovolemia, geriatric, Pregnancy, lactation

Antidiuretic Hormone Antagonists

Conivaptan, tolvaptan

<u>Renal effects</u>	<u>MOA</u>	<u>Therapeutic Uses</u>	<u>Adverse effects</u>
<ul style="list-style-type: none">Increased water diuresis (these drugs are also called aquaretics)Water diuresis increases more than salt diuresis (in this way hyponatremia is relieved).Increased renal excretion of: Na⁺, K⁺, Ca⁺⁺Urine osmolality: decreasedOther effectsConivaptan is a strong inhibitor of CYP3A4	<ul style="list-style-type: none">Competitive antagonists at vasopressin receptors (conivaptan at V1a and V2, tolvaptan at V2)	<ul style="list-style-type: none">Syndrome of inappropriate ADH secretion (when water restriction failed to correct the disorder)Chronic euvolemic hyponatremia	<ul style="list-style-type: none">Infusion-site reactions (with conivaptan)Nephrogenic diabetes insipidusPostural hypotension (if hypovolemia develops)Hypokalemia (. 9%)